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Orthostatic hypotension and physical functioning in older adults: A systematic review and meta-analysis

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ABSTRACT

Background: Orthostatic hypotension (OH) may negatively affect physical functioning and aggravate morbidities, but existing evidence is contradictory.

Methods: MEDLINE (from 1946), PubMed (from 1966) and EMBASE databases (from 1947) were systematically searched for studies on the association of OH and physical functioning in older adults, categorized as: balance, gait characteristics, walking speed, Timed Up and Go time, handgrip strength (HGS), physical frailty, exercise tolerance, physical activity, activities of daily living (ADL), and performance on the Hoehn and Yahr scale (HY) and Unified Parkinson's Disease Rating Scale (UPDRS). Study quality was assessed using the Newcastle Ottawa Scale.

Results: Forty-two studies were included in the systematic review (29,421 individuals) and 29 studies in the meta-analyses (23,879 individuals). Sixteen out of 42 studies reported a significant association of OH with worse physical functioning. Meta-analysis showed a significant association of OH with impaired balance, ADL performance and HY/UPDRS III performance, but not with gait characteristics, mobility, walking speed, TUG, HGS, physical frailty, exercise tolerance, physical activity and UPDRS II performance.

Conclusions: OH was associated with impaired balance, ADL performance and HY/UPDRS III performance, but not with other physical functioning categories. The results suggest that OH interventions could potentially improve some aspects of physical functioning.

1. Introduction

Orthostatic hypotension (OH) is a serious disorder, associated with increased risk of cardiovascular disease, impaired renal function, dementia, falls, and death (Frith et al., 2016; Ong et al., 2017; Ricci et al., 2015; Saedon et al., 2016; Yasa et al., 2018). OH is defined as a systolic blood pressure drop of at least 20 mmHg and/or a diastolic blood pressure drop of at least 10 mmHg within 3 min after standing up according to the consensus definition (Freeman et al., 2011). The prevalence of OH was reported to range from 9 to 30% in community-dwelling adults aged above 65 years (Ong et al., 2017; Veronese et al., 2015) to more than 50% in nursing home residents (Lagro et al., 2012). OH is particularly prevalent in patients with Parkinson's Disease (PD, 47–58%) (Allcock et al., 2004; Senard et al., 1997).

OH may negatively affect physical functioning (e.g. balance, gait characteristics, walking speed, exercise tolerance and activities of daily living (ADL)) in older adults through different mechanisms: 1) acute decreased brain perfusion and oxygenation within minutes after postural change (Mager, 2012); 2) chronic brain pathology, such as brain atrophy, microbleeds and white matter brain lesions (Aoki et al., 2013; Ben Salem et al., 2008; Starr et al., 2003); 3) impaired muscle microcirculation, causing poor muscle endurance and pain in neck, buttock

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and calf muscles (Bleasdale-Barr and Mathias, 1998; Degens et al., 2006; Humm et al., 2011; Robbins et al., 2011). Therefore, OH may cause deterioration of physical functioning. However, evidence on the association of OH and physical functioning in older adults is contradictory, as an association with both impaired (Ensrud et al., 1992; Matsubayashi et al., 2017) and better (Ooi et al., 1997) physical functioning was reported.

To obtain insight in the clinical relevance of OH, this systematic review and meta-analysis provides a summary of the existing evidence on the association of OH and physical functioning in older adults.

2. Methods

The review protocol was registered in the PROSPERO International prospective register of systematic reviews (CRD42017060134). MEDLINE (from 1946), PubMed (from 1966) and EMBASE databases (from 1947) were systematically searched for studies published until February 2017 and investigating OH and physical functioning in cohorts of older adults (> 65 years). The search strategy is presented in Appendix A and includes the keywords ‘orthostatic hypotension’, ‘balance’, ‘gait’, ‘mobility’, ‘walking’, ‘strength’, ‘exercise’ and ‘activity’.

2.1. Study selection

Studies were organized and managed using EndNote (Version: X8.2. Clarivate Analytics, Philadelphia, USA). After removing duplicates, studies were assessed for potential eligibility by two different reviewers (AM and PTSBH) by screening titles and abstracts. Potentially eligible studies were then screened full-text by the same reviewers. Studies were considered eligible if the following criteria were met: 1) publication in English, 2) mean or median age of the study cohort was 65 years or higher, 3) blood pressure was assessed before and after postural change and 4) its association with physical functioning was assessed. Conference abstracts, reviews, editorials and letters to the editor were excluded. Any disagreements between the reviewers were resolved by discussion with a third author (EMR, CGM or ABM). If study results from the same cohort were published in duplicate, one study was included in the systematic review. The references of eligible studies were screened for additional studies meeting the criteria.

2.2. Data extraction

The following data were extracted independently by two authors (AM and PTSBH): first author; year of publication; size, age and sex of the included population; study design; study population; OH definition; OH test conditions (i.e. duration of resting period before postural change and type of postural change); blood pressure measurement (continuous or intermittent) and timing; OH prevalence; assessment method of physical functioning; physical functioning.

Data on the consensus definition of OH (systolic blood pressure drop > 20 mmHg or diastolic blood pressure drop > 10 mmHg) or systolic OH (systolic blood pressure drop > 20 mmHg) were extracted if different definitions for OH were used in one study (Freeman et al., 2011). Data on continuously measured blood pressure was extracted rather than intermittently measured blood pressure, as continuous blood pressure measurements are more sensitive for the diagnosis of OH (Frith, 2015; Pasma et al., 2014). Results of active stand tests rather than other types of postural change (e.g. head up tilt test) were extracted. In studies reporting different balance test outcomes for the same population, results of objective tests were extracted rather than subjective tests and results of challenging tests rather than easier tests (e.g. tandem stance rather than side-by-side stance).

In three studies, results were only depicted in figures. The authors of these studies were contacted for the exact results, two of whom responded (Merola et al., 2016; Pasma et al., 2014). In the other case, we extracted data from the figures (Shen et al., 2015a). Study populations were categorized as community-dwelling adults, outpatients, geriatric inpatients, nursing home residents or patients with PD or parkinsonism (i.e. atypical parkinsonism or multiple system atrophy).

2.3. Study quality

Study quality of the included studies was assessed independently by two authors (AM and PTSBH) using the nine-point Newcastle Ottawa Scale (Margulis et al., 2014), higher scores indicating lower risk of bias. The NOS scale for cohort studies rather than the adapted NOS scale for cross-sectional studies was used to enable rating cross-sectional studies along with prospective studies. Studies with scores of 0–3, 4–6 and 7–9 points were considered low, moderate and high quality, respectively. The specified Newcastle Ottawa Scale for this study is provided in Appendix B.

2.4. Physical functioning categories

Physical functioning was grouped in 12 categories: 1) balance (i.e. self-reported or objectively assessed), 2) gait characteristics (i.e. gait initiation, symmetry, gait regularity, trunk sway and path width assessed by a healthcare professional), 3) mobility (i.e. self-reported mobility and use of walking aids), 4) walking speed (i.e. walking speed on test path length between 4 m–500 m), 5) Timed Up and Go time (TUG, i.e. time needed to stand up, walk around a cone and sit down), 6) handgrip strength (HGS, i.e. hand grip strength of strongest hand), 7) physical frailty (i.e. frailty assessed using the Fried frailty scale), 8) exercise tolerance (i.e. peak O_2 consumption during exercise or performance on exercise scale for specific diseases), 9) physical activity (i.e. self-reported time spent non-sedentary), 10) activities of daily living (ADL) performance (i.e. self-reported ADL independence), 11) UPDRS II ADL performance (i.e. performance on the ADL subscale of the Unified Parkinson’s Disease Rating Scale (UPDRS II)), and 12) HY / UPDRS III performance (i.e. performance on the Hoehn and Yahr (HY) or UPDRS III scales, assessing motor performance in Parkinson’s Disease)

2.5. Study selection for meta-analysis

Studies were included in the meta-analysis if 1) studies had the same study design (i.e. cross-sectional versus longitudinal); 2) physical functioning was reported for subjects with OH compared to those without OH using odds ratio’s (ORs), means, medians or the prevalences of the OH and the non−OH group; 3) the reported physical function outcome could be classified into one physical functioning category.

2.6. Meta-analysis

For dichotomous physical functioning outcomes, the unadjusted odds ratio (OR) was used or the OR was computed from reported prevalence data in the group with and without OH. For continuous physical functioning outcomes, the means and standard deviations (SD) were used to compute standardized mean differences and the logarithm of the OR (logOR), to enable pooling with dichotomous outcomes according to the Hasselblad and Hedges method (Chinn, 2000; Da Costa et al., 2012). Medians, ranges or interquartile ranges were converted to means and SDs (Wan et al., 2014) in studies with more than 50 subjects (Kwak and Kim, 2017).

Meta-analyses, including at least two studies, were performed using Review Manager (RevMan. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random effects model was used, as studies were different with respect to the used OH definition, blood pressure measurement protocol and physical functioning measurement, implying heterogeneity (Borenstein et al., 2010). Apart from the pooled analyses per category of physical functioning,

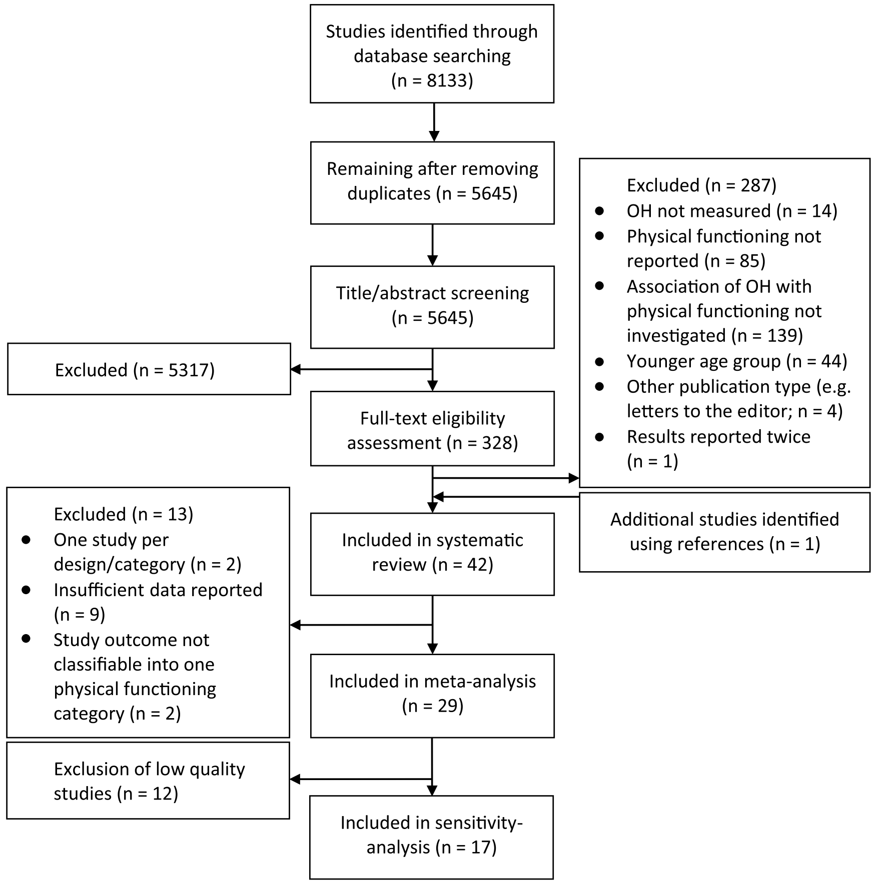

Fig. 1. Study identification and selection.

subgroup analyses were performed per population. Heterogeneity was expressed using the I^2 statistic (< 25% low; < 50%: moderate; > 50%: high). If studies showed a discrepancy between the statistical significance as reported and as computed in the meta-analysis, a sensitivity analysis was performed, excluding these studies. Likewise, a sensitivity analysis excluding low quality studies was performed. P-values below 0.05 and 0.1 were considered significant and a trend, respectively. An estimate of publication bias was calculated using Egger's test for meta-analyses including at least ten studies, using a significance level of 10% (Egger et al., 2015; Sterne et al., 2011).

3. Results

Fig. 1 shows the study identification and selection flowchart. The search resulted in 5645 studies. Of these studies, 328 full text articles were retrieved and screened for study eligibility. Forty-two studies were included in the systematic review. Data extracted from 29 studies were included in a meta-analysis.

3.1. Systematic review

Table 1 provides the study characteristics of each included study. The studies included a total of 29,421 individuals. Thirty-nine studies were cross-sectional, 2 were prospective and 1 was retrospective. Community-dwelling populations were investigated in 13 studies, outpatients in 9 studies, geriatric inpatients in 9 studies, nursing home residents in 3 studies and patients with PD or parkinsonism in 8 studies. Thirty studies used the consensus definition of OH, 7 studies used systolic OH and 5 studies used other OH definitions.

Table 2 presents an overview of the associations of OH and physical functioning. The extracted data are provided in Appendix C. OH was associated with physical functioning in 18/43 of the studies: impaired balance (7/14), gait abnormalities (1/5), mobility (worse: 3/9, better: 1/9), slower walking speed (2/7), TUG time (slower: 0/6, faster: 1/6) and lower HGS (1/4). Associations between OH and physical frailty, exercise tolerance or physical activity were significant in none of the studies. OH was associated with physical functioning in 7/17 (worse: 6/17, better: 1/17) of the studies assessing ADL performance, 1/3 of the studies using the UPDRS II ADL scale and 2/7 of studies using the HY/UPDRS III performance scale.

Table 3 presents the study quality for all included studies. Nineteen studies were of low quality, 23 studies were of moderate quality and none of the studies were of high quality.

3.2. Meta-analysis

A total of 23,879 individuals from 29 cross-sectional studies were included in the meta-analyses. None of the longitudinal studies were included. Nineteen of the included studies used the consensus definition of OH, 6 studies used the systolic OH definition and 4 studies used other definitions. Appendix D shows the list of physical functioning measures per physical functioning category.

Fig. 2 shows the overall pooled effect estimates of the association of OH with physical functioning stratified by physical functioning categories, and the sensitivity analysis for study quality. Appendix E provides the forest plots showing individual study data, stratified by study population, for each physical functioning category. OH was significantly associated with objective or self-reported balance impairment in all populations (Fig. E1, OR 0.57, 95% CI 0.42-0.78). Seven studies reported objective balance measures (overall OR 0.43, 95% CI 0.27 – 0.69) (Aydin et al., 2017; Cordeiro et al., 2009; Gaxatte et al., 2017; Hohler et al., 2012; Pasma et al., 2014; Shen et al., 2015b; Soysal et al.,

Table 1
Study characteristics, stratified by population.

First author, year of publication	N	Mean age (SD or range)	Male (%)	Design	OH definition	Resting period (min)	Postural change	BP measure-ment	BP timing (min)	Included in meta-analysis
Community-dwelling										
Ensrud et al., 1992	9704	71.7 (65-99)	0	Cs	sOH	5	AS	I	1	Yes
Formes et al., 2010	19	67.5 (3.8)	63.5	Cs	NR	20	LBNP	C	36	No
Guo et al., 2003	234	70	0	Cs	OH	NR	AS	NR	NR	No
	88			P	OH	NR	AS	NR	NR	No
Kobayashi and Yamada, 2012	86	73.1 (6.3)	24.4	Cs	OH	10	HUT	C	3	Yes
Mader et al., 1987	300	69.8 (56-93)	23.0	Cs	sOH	5	AS	I	1	Yes
Masaki et al., 1998	3741	(71-93)	100	Cs	OH	15	AS	I	3	No
Matsubayashi et al., 2017	334	80.0 (5.0)	45.5	Cs	sOH	5	AS	I	1; 2	Yes
Rockwood et al., 2012	1347	83.3 (6.4)	50.5	Cs	OH	NR	AS	I	< 3	Yes
Romero-Ortuno et al., 2011	442	72	28	Cs	OH	10	AS	C	3	Yes
Rutan et al., 1992	4931	64.3*	43.5	Cs	OH	NR	AS	I	3	Yes
Tang et al., 2012	49	66.0 (7.0)	59	Cs	OH	10	PS	I	1-3†	No
Tilvis et al., 1996	569	80.0 (4.1)	NR	Cs	OH	5	AS	I	1	No
Zhu et al., 2016	364	74.6 (64-98)	49.5	Cs	OH	5	AS	I	1; 3	Yes
Outpatients										
Aydin et al., 2017	290	74.8 (8.7)	40.7	Cs	OH	5	AS	I	3	Yes
Cordeiro et al., 2009	91	74.4 (5.9)	34.1	Cs	NR	NR	AS	I	3	Yes
Gaxatte et al., 2017	833	80.4 (7.4)	26.9	Cs	OH	10	AS	I	1; 3	Yes
Oishi et al., 2016	64	84.0 (6.0)	31.3	Cs	OH	NR	AS	I	0; 1; 3; 5	Yes
Pasma et al., 2014	58	80.6 (7.0)	43.1	Cs	OH or iOH	5	AS	C	3	Yes
Press et al., 2016	571	83.0 (6.1)	35.9	Cs	OH	10	AS	I	1; 3	Yes
Soysal et al., 2014	546	73.3 (8.8)	39.4	Cs	OH	10	AS	I	1; 3	Yes
Soysal et al., 2016	407	75.1 (8.4)	37.3	Cs	OH	10	HUT	I	1; 3; 5	Yes
Susman, 1989	100	73 (65-90)	38	Cs	OH	5	AS	I	1; 2	No
Geriatric inpatients										
Aries et al., 2012	167	68.5 (15.2)	54.5	P	OH	3	AS	I	3	No
Bendini et al., 2007	36	80.5 (6.2)	27.8	Cs	OH	NR	AS	I	1; 3	No
Coutaz et al., 2012	340	80 (8.2)	31.5	Cs	OH	30	AS	I	1; 3; 5	Yes
Jodaitis et al., 2015	285	85.0 (5.0)	46	R	OH	NR	SS	I	0; 1; 3	No
Kihara et al., 1998	15	85.1 (2.1)	40	Cs	$OH_{30/15}$	NR	HUT	C	5	Yes
MacLennan et al., 1987	100	82.4 (64-94)	0	Cs	sOH	NR	AS	NR	NR	Yes
Shen et al., 2015a, 2015b	176	76.7 (6.6)	57.4	Cs	OH	5	AS	I	1; 3	Yes
Siennicki-Lantz et al., 1999	27	82.2 (3.6)	0	Cs	sOH	NR	HUT	I	0-8†	No
Vloet et al., 2005	85	80.0 (1.0)	51.7	Cs	sOH	5	AS	I	1; 3	Yes
Nursing home residents										
Gray-Miceli et al., 2012	77	90.0 (5.8)	18.0	Cs	OH	NR	NR	NR	NR	No
Gray-Miceli et al., 2016	47	90.7 (5.8)	26.0	Cs	OH	NR	NR	NR	NR	No
Ooi et al., 1997	911	83.1 (10.9)	20.0	Cs	OH	NR	AS	I	1; 3	Yes
Patients with PD or parkinsonism										
Allcock et al., 2006	159	70.6	61	Cs	OH	10	AS	I	NR	Yes
Ha et al., 2011	1318	68.8 (30.7)	61.4	Cs	OH+	NR	AS	NR	NR	Yes
Hohler et al., 2012	44	NR	61.4	Cs	OH	NR	SS	I	1; 3	Yes
Matinolli et al., 2009	120	68.2 (10.1)	66.7	Cs	OH	NR	AS	I	1-3†	Yes
Matsui et al., 2006	40	71.1 (8.3)	17.5	Cs	sOH	10	AS	I	0-3†	Yes
Merola et al., 2016	121	66.7 (8.9)	57.0	Cs	OH	10	AS	I	1; 3	Yes
Perez-Lloret et al., 2012	103	66.0 (1.0)	73	Cs	OH	5	AS	I	1-3†	No
Sithinamsuwan et al., 2010	82	69.2 (10.3)	69.5	Cs	OH	5	AS	I	3	Yes

Cs: cross-sectional; P: prospective; R: retrospective; OH: consensus definition of orthostatic hypotension; $OH_{30/15}$: drop of 30 and 15 mmHg in systolic or mean blood pressure, respectively; OH+: OH with symptoms; iOH: initial OH (systolic blood pressure drop of at least 40 mmHg and/or a diastolic blood pressure drop of at least 20 mmHg within 15 s after standing); sOH: systolic blood pressure drop of at least 20 mmHg; NR: not reported; AS: active stand; SS: sit to stand; PS: passive sit; HUT: head up tilt; LBNP lower body negative pressure (i.e. a simulation of postural change); BP: blood pressure; C: continuous; I: intermittent; BP timing: time of blood pressure measurement after postural change. *Percentage of population between 65 and 79 years. †measured with intervals of one minute.

2014) and four studies reported subjective balance measures (overall OR 0.83, 95% CI 0.71–0.97) (Mader et al., 1987; Oishi et al., 2016; Rutan et al., 1992; Soysal et al., 2016). OH was not associated with gait characteristics, mobility, walking speed, TUG, HGS, physical frailty and physical activity (Figs. E2–E8). OH was significantly associated with impaired ADL performance (Fig. E9, OR 0.63, 95% CI 0.45-0.88), but not with UPDRS II ADL performance (Fig. E10, OR 0.41, 95% CI 0.14–1.21). OH was significantly associated with worse HY/UPDRS III performance (Fig. E11, OR 0.67, 95% CI 0.54-0.82).

Two studies in the balance category showed a discrepancy between reported statistical significance and statistical significance calculated in the meta-analysis (Rutan et al., 1992; Soysal et al., 2014). Excluding these from the meta-analysis resulted in a minor change to the overall effect in the balance category (OR 0.49, 95% CI 0.30–0.79). Excluding one study from the HY/UPDRS III performance category for the same reason (Merola et al., 2016) changed the overall OR in this category to 0.69 (95% confidence interval 0.55–0.87). The sensitivity analysis for study quality (exclusion of 12 low quality studies) did not differ from the main analysis with respect to the significance of the associations of OH with any of the physical functioning categories, except for HY/UPDRS III performance (OR 0.64, 95% CI 0.34–1.19).

Studies finding an association of OH with ADL dependence did not include more patients with cognitive impairment than studies finding no association. The prevalence of dementia was 42.9% in one study reporting an association (Gaxatte et al., 2017) compared to 27.0–44.9% in three studies reporting no association (Aydin et al., 2017; Jodaitis et al., 2015; Siennicki-Lantz et al., 1999). The mean Mini Mental State Examination score was 17.6–25.8 points in four studies finding an

Table 2
Prevalence of OH and associations of OH and physical functioning.

First author	OH prevalence (%)	Balance	Gait characteristics	Mobility	Walking speed	TUG	HGS	Physical frailty	Exercise tolerance	Physical activity	ADL performance	UPDRS II	HY/UPDRS III
Community-dwelling													
Ensrud et al., 1992	14.0	.	.	.	.	.	.	.	.	.	_	.	.
Formes et al., 2010	.	.	.	.	.	.	.	.	=	.	.	.	.
Guo et al., 2003[*]	11.4	++	.	++	++	.	.	.	.	.	.	.	.
Guo et al., 2003[*]	.	=	.	=	=	.	.	.	.	.	.	.	.
Kobayashi and Yamada, 2012	33.7	.	.	.	=	.	=	.	.	.	.	.	.
Mader et al., 1987	10.7	=	.	.	.	.	.	.	.	.	.	.	.
Masaki et al., 1998	6.9	.	.	.	++	.	++	.	.	.	.	.	.
Matsubayashi et al., 2017	6.6	.	.	.	.	=	.	.	.	.	+	.	.
Rockwood et al., 2012	28.9	.	.	.	.	.	.	=	.	.	.	.	.
Romero-Ortuno et al., 2011	94.1	.	.	.	=	.	=	=	.	=	.	.	.
Rutan et al., 1992	16.2	=[†]	.	+	.	.	.	.	.	.	=	.	.
Tang et al., 2012	14.2	.	.	.	.	.	.	.	=	.	.	.	.
Tilvis et al., 1996	21.4	.	.	.	.	.	.	.	=	.	.	.	.
Zhu et al., 2016	11.0	.	.	=	.	.	.	.	.	=	.	.	.
Outpatients													
Aydin et al., 2017	37.0	=	=	.	.	.	.	.	.	.	=	.	.
Cordeiro et al., 2009	29.1	+	.	.	.	=	.	.	.	.	.	.	.
Gaxatte et al., 2017	23.9	=	=	.	.	=	.	.	.	.	+	.	.
Oishi et al., 2016	26.6	=	.	.	.	_	.	.	.	.	.	.	.
Pasma et al., 2014	57.0	+	.	.	.	.	.	.	.	. .		.	.
Press et al., 2016	32.2	.	.	.	.	.	.	.	.	.	=	.	.
Soysal et al., 2014	27.5	=[‡]	=	.	.	.	.	.	.	.	+	.	.
Soysal et al., 2016	22.1	=	.	.	.	.	.	.	.	.	.	.	.
Susman, 1989	31.0	.	.	.	.	.	.	.	.	.	=	.	.
Geriatric inpatients													
Aries et al., 2012	13.1	.	.	.	.	.	.	.	.	.	=	.	.
Bendini et al., 2007	25.0	.	.	.	.	.	.	.	.	.	+	.	.
Coutaz et al., 2012	42.4	.	.	.	.	.	.	.	.	.	=	.	.
Jodaitis et al., 2015	41.0	.	.	.	.	.	.	.	.	.	=	.	.
Kihara et al., 1998	40.0	.	.	.	.	.	.	.	.	.	=	.	.
MacLennan et al., 1987	34.7	.	.	=	.	.	.	.	.	.	.	.	.
Shen et al., 2015a, 2015b	20.5	++	=	=	=	.	=	.	.	.	.	.	.
Siennicki-Lantz et al., 1999	48.1	.	.	.	.	.	.	.	.	.	=	.	.
Vloet et al., 2005	56.5	.	.	=	.	.	.	.	.	.	.	.	.
Nursing home residents													
Gray-Miceli et al., 2012	9.3	++	.	.	.	.	.	.	.	.	.	.	.
Gray-Miceli et al., 2016	15.4	+	++	.	.	.	.	.	.	.	.	.	.
Ooi, 1997	51.5	.	.		.	.	.	.	.	.	=	.	.
Patients with PD or parkinsonism													
Allcock et al., 2006	50.3	.	.	.	.	.	.	.	.	.	.	.	=
Ha et al., 2011	19.0	.	.	.	.	.	.	.	.	.	.	.	+[§]
Hohler et al., 2012	39.0	+	.	.	=[‡]	=	.	.	.	.	+	.	.
Matinolli et al., 2009	52.5	.	.	=	=	=	.	.	.	=	.	=	=
Matsui et al., 2006	62.5	.	.	.	.	.	.	.	.	.	.	.	=
Merola et al., 2016	30.6	.	.	+	.	.	.	.	.	.	+	+	=[†]
Perez-Lloret et al., 2012	36.9	.	.	.	.	.	.	.	.	.	.	=[‖]	=[‖]
Sithinamsuwan et al., 2010	40.2	.	.	.	.	.	.	.	.	.	.	.	+

Results are denoted with '++' ($p < 0.01$) or '+' ($p < 0.05$) if OH was associated with worse physical functioning, '=' if no association was found, '_' ($p < 0.05$) if OH was associated with better physical functioning and '.' if no data were available. [*]The rows correspond to the cross-sectional and prospective part of the study, respectively. The listed results are from a combined task involving walking speed, balance and mobility. [†]Adjusted result shown is not significant, but unadjusted result is significant. [‡]Statistical significance calculated in the meta-analysis is different from statistical significance reported in the study due to differences in statistical analysis. [§]This association was only found for the subgroup of patients with PD. [‖]Combined UPDRS II and III scales.

Table 3
Study quality assessed using the Newcastle Ottawa Scale.

First author	Representativeness of cohort	Non-exposed cohort from same community	BP measured continuously	Consensus definition of OH	Adjusted for age/sex	Adjusted for other factors	Objective outcome	Follow up > 6 months	< 20% loss to follow up	Total score
Community-dwelling										
Ensrud et al., 1992	*	*	–	–	*	–	–	–	–	3
Formes et al., 2010	*	–	*	–	–	–	–	–	–	2
Guo et al., 2003	*	*	–	*	–	–	*	*	–	5
Kobayashi and Yamada, 2012	*	*	*	*	–	–	*	–	–	5
Mader et al., 1987	*	*	–	–	–	–	–	–	–	2
Masaki et al., 1998	*	–	–	*	–	–	*	–	–	3
Matsubayashi, 2017	*	*	–	–	–	–	*	–	–	3
Rockwood, 2012	*	*	–	*	–	–	*	–	–	4
Romero-Ortuno et al., 2011	*	*	*	*	–	–	*	–	–	5
Rutan et al., 1992	*	*	–	*	*	*	–	–	–	5
Tang et al., 2012	*	*	–	*	–	*	*	–	–	5
Tilvis et al., 1996	*	*	–	*	*	–	*	–	–	5
Zhu et al., 2016	*	*	–	*	–	–	–	–	–	3
Outpatients										
Aydin et al., 2017	*	*	–	*	–	–	*	–	–	4
Cordeiro et al., 2009	*	*	–	–	–	–	*	–	–	3
Gaxatte et al., 2017	*	*	–	*	–	–	*	–	–	4
Oishi et al., 2016	*	*	–	*	–	–	*	–	–	4
Pasma et al., 2014	*	–	*	*	*	–	*	–	–	5
Press et al., 2016	*	*	–	*	–	–	–	–	–	3
Soysal et al., 2014	*	*	–	*	–	–	*	–	–	4
Soysal et al., 2016	*	*	–	*	–	–	*	–	–	4
Susman, 1989	*	*	–	*	–	–	–	–	–	3
Geriatric inpatients										
Aries et al., 2012	*	–	–	*	–	–	*	–	–	3
Bendini et al., 2007	*	–	–	*	*	–	–	–	–	3
Coutaz et al., 2012	*	*	–	*	–	–	*	–	–	4
Jodaitis et al., 2015	*	*	–	*	–	*	–	–	–	4
Kihara et al., 1998	*	–	*	–	–	–	–	–	–	2
MacLennan et al., 1987	*	*	–	–	–	–	*	–	–	3
Shen et al., 2015a, 2015b	*	*	–	*	*	–	*	–	–	5
Siennicki-Lantz et al., 1999	*	*	–	–	–	–	–	–	–	2
Vloet et al., 2005	*	*	–	–	–	–	–	–	–	2
Nursing home residents										
Gray-Miceli et al., 2012	*	*	–	*	–	–	*	–	–	4
Gray-Miceli et al., 2016	*	*	–	*	–	–	–	–	–	3
Ooi et al., 1997	*	*	–	*	*	*	–	–	–	5
Patients with PD or parkinsonism										
Allcock et al., 2006	*	–	–	*	–	–	*	–	–	3
Ha et al., 2011	*	*	–	–	–	–	*	–	–	3
Hohler et al., 2012	*	*	–	*	–	–	*	–	–	4
Matinolli et al., 2009	*	*	–	*	–	–	*	–	–	4
Matsui et al., 2006	*	*	–	–	–	–	*	–	–	3
Merola et al., 2016	*	*	–	*	–	*	*	–	–	5
Perez-Lloret et al., 2012	*	*	–	*	*	*	*	–	–	6
Sithinamsuwan et al., 2010	*	*	–	*	–	–	*	–	–	4

'*' Indicates an attributed point. BP: blood pressure.

association (Bendini et al., 2007; Hohler et al., 2012; Matsubayashi et al., 2017; Soysal et al., 2014) versus 21.0–25.0 points in two studies finding no association (Coutaz et al., 2012; Press et al., 2016).

3.3. Heterogeneity and publication bias

Heterogeneity was high for the results of balance, mobility, ADL performance and UPDRS II ADL performance; moderate for TUG; and low for gait characteristics, walking speed, HGS, physical frailty, physical activity, and HY and UPDRS III performance. Egger's regression test for balance and ADL performance showed statistical evidence for publication bias of ADL performance ($p = 0.972$ and $p = 0.045$, respectively).

4. Discussion

Less than half of studies included in the systematic review showed an association between OH and physical functioning. In the meta-

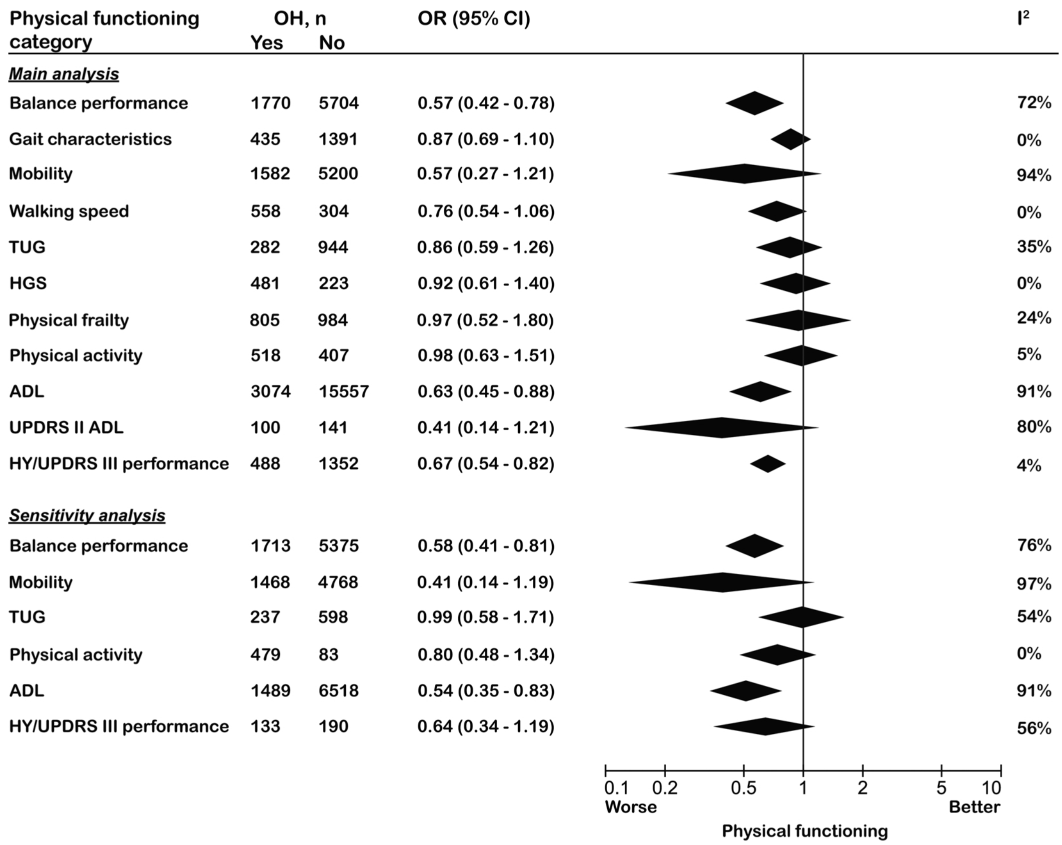

Fig. 2. Pooled estimates of the association of OH and physical functioning, per physical functioning category. The main analysis reflects all studies included in the meta-analysis. The sensitivity analysis for study quality lists the pooled estimates of the association of OH and physical functioning after exclusion of low quality studies (only if applicable). TUG: Timed Up and Go; HGS: handgrip strength; ADL: activities of daily living; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr Scale.

analyses, a significant association of OH with impaired balance was found, whereas OH was not associated with gait characteristics, mobility, walking speed, TUG, HGS, physical frailty and physical activity. OH was associated with impaired ADL and HY/UPDRS III performance, but not with UPDRS II ADL performance. Most studies were of moderate quality.

To the best of our knowledge, no meta-analysis addressing the association between OH and physical functioning in older adults has been published. Previous reviews on OH reported an association with falls and mortality (Angelousi et al., 2014; Hartog et al., 2017; Shaw and Claydon, 2014). The association of OH with physical functioning found in the present study was modest, showing significant associations only in some physical functioning categories. As no more than one longitudinal study was available per physical functioning category, no longitudinal studies were included in the meta-analysis.

The significant association of OH and impaired balance is in line with a previous study reporting an association between OH and a shorter time to a first fall, suggesting impaired balance as a possible mechanism (Hartog et al., 2017). The association found in the present study was robust due to the large number of individuals included in the meta-analysis and the congruence of most studies with respect to the direction of the effect. Heterogeneity in this category was high due to pooling of objective and subjective balance measures. However, the overall association was robust, as separate meta-analyses for studies reporting objective and subjective measures both showed an association of OH with impaired balance.

No association of OH was found with gait characteristics, mobility, walking speed and TUG, HGS, physical frailty and physical activity, which may be explained by the large study diversity and poorly standardized measurement protocols with respect to OH definition, blood pressure measurement protocol and physical functioning outcome, and by a moderate overall study quality.

OH was significantly associated with impaired ADL performance in the meta-analysis, which included a large number of individuals. However, results on Egger's test indicate that this association may have been influenced by publication bias, suggesting exclusion of negative studies.

The found association of OH with HY/UPDRS III performance should be interpreted cautiously, as it did not remain significant in the sensitivity analysis for study quality.

4.1. Potential pathophysiological mechanisms involved

Mechanisms causing OH may be neurogenic or non-neurogenic (Chisholm and Anpalahan, 2017). Neurogenic causes are likely to underlie OH in patients with PD and parkinsonism, as these diseases affect the autonomic nervous system. In other patients, medication (e.g. vasodilators and diuretics), volume depletion and deconditioning are likely to contribute to OH, as these are common in older adults, especially when institutionalized (Piko and Bevc, 2017; van der Velde et al., 2007).

Various pathophysiological mechanisms may underlie the found associations of OH with impaired physical functioning, though the present study does not demonstrate these. White matter brain lesions are associated with OH (Aoki et al., 2013; Ben Salem et al., 2008; Starr et al., 2003) and may lead to impaired balance (Aoki et al., 2013; Demain et al., 2014). They are also associated with cognitive impairment (David et al., 2016; Malek et al., 2016), which might be an intermediate factor between OH and impaired ADL performance, as cognitive impairment is associated with both OH and impaired ADL performance (Bocti et al., 2017; Centi et al., 2017; De Vriendt et al., 2015; Dodge et al., 2005; Huang et al., 2017; Mehrabian et al., 2010; Sands et al., 2002). However, the data of the current study do not provide evidence for cognitive impairment as an intermediate factor. A common neural degenerative process may underlie the association of OH with HY/UPDRS III performance, as PD both affects the autonomic system, causing OH, and the dopaminergic neurons in the nigrostriatal system, causing worse HY/UPDRS III performance (Freeman, 2008; Jain and Goldstein, 2012).

4.2. Strengths and limitations

The strength of this systematic review is that data were reported on a variety of physical functioning categories and analyses were stratified for different populations. However, the diversity of studies within categories of physical functioning has increased the heterogeneity. Cross-sectional studies could not be given points on the two items related to follow up on the NOS scale. The NOS scale was used to enable rating cross-sectional studies along with prospective studies. As non-adjusted data were included in the meta-analyses, a confounding role of age, sex, height and other factors cannot be excluded. No conclusions can be drawn about the longitudinal association of OH with physical functioning and potential causality underlying the found associations.

5. Conclusions

This systematic review and meta-analysis shows that OH is associated with impaired balance (objective or self-reported), ADL performance and HY/UPDRS III performance, but not with gait characteristics, mobility, walking speed, TUG, HGS, physical frailty, exercise tolerance, physical activity and UPDRS II performance, based on studies with overall moderate quality. Standardized OH and physical functioning measurement protocols are needed to enable more accurate investigation of the relationship between OH and physical functioning. Future research should investigate the role of OH as a predictor of physical functioning decline in longitudinal studies and address the effect of OH interventions to potentially improve physical functioning.

Author Contributions

ABM and CGM conceived the study. AM and PTSBH planned the study and AM developed the search strategy. AM and PTSBH performed the screening and data extraction. Doubts about inclusion were resolved by ABM, CGM or EMR. AM and PTSBH performed the data-analysis and AM took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. ABM is the guarantor of the review.

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Declarations of interest

None.

Acknowledgements

We thank Rikie Deurenberg from the Radboud University Library, who greatly assisted with the construction of the search strategy.

Appendix A

MEDLINE search strategy

1 exp Hypotension, Orthostatic/ (5281)
2 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kf. (407)
3 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (6866)
4 or/1-3 (9329)
5 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (585748)
6 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kf. (20955)
7 exp exercise/ or exp exercise test/ or exp exercise tolerance/ or exp physical endurance/ or exp physical fitness/ or exp walk test/ or exp muscle strength/ or exp hand strength/ or exp gait/ or exp postural balance/ or exp "activities of daily living"/ or exp geriatric assessment/ or exp frail elderly/ or exp Accidental Falls/ (345254)
8 or/5-7 (846790)
9 4 and 8 (1695)
10 exp Hypotension, Orthostatic/ (5281)
11 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kf. (407)
12 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (6866)
13 or/10-12 (9329)
14 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or

(geriatric evaluation adj2 management*) or frail* or fall*).tw. (585748)
15 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kf. (20955)
16 exp exercise/ or exp exercise test/ or exp exercise tolerance/ or exp physical endurance/ or exp physical fitness/ or exp walk test/ or exp muscle strength/ or exp hand strength/ or exp gait/ or exp postural balance/ or exp "activities of daily living"/ or exp geriatric assessment/ or exp frail elderly/ or exp Accidental Falls/ (345254)
17 or/14-16 (846790)
18 13 and 17 (1695)

PubMed search strategy

1 ((((((((postural hypotension[Other Term]) OR postural blood pressure[Other Term]) OR orthostatic hypotension[Other Term]) OR orthostatic blood pressure[Other Term]) OR orthostasis[Other Term])))) OR (((((postural hypotension[Title/Abstract]) OR postural blood pressure[Title/Abstract]) OR orthostatic hypotension[Title/Abstract]) OR orthostatic blood pressure[Title/Abstract]) OR orthostasis[Title/Abstract]))) OR "Hypotension, Orthostatic"[mesh] (9146)
2 (((((postural hypotension[Other Term]) OR postural blood pressure[Other Term]) OR orthostatic hypotension[Other Term]) OR orthostatic blood pressure[Other Term]) OR orthostasis[Other Term])) (245)
3 (((((postural hypotension[Title/Abstract]) OR postural blood pressure[Title/Abstract]) OR orthostatic hypotension[Title/Abstract]) OR orthostatic blood pressure[Title/Abstract]) OR orthostasis[Title/Abstract]) (6694)
4 1 OR 2 OR 3
5 ((((((((((((exercise[MeSH Terms]) OR exercise test[MeSH Terms]) OR exercise tolerance[MeSH Terms]) OR physical endurance[MeSH Terms]) OR physical fitness[MeSH Terms]) OR walk test[MeSH Terms]) OR muscle strength[MeSH Terms]) OR hand strength[MeSH Terms]) OR gait [MeSH Terms]) OR postural balance[MeSH Terms]) OR activities of daily living[MeSH Terms]) OR geriatric assessment[MeSH Terms]) OR frail elderly[MeSH Terms]) OR Accidental Falls[MeSH Terms] (339711)
6 ((((((((((((((((((Exercise[Other Term] OR Exercises[Other Term]) OR Physical performance[Other Term]) OR Physical mobility[Other Term]) OR Physical endurance[Other Term]) OR Physical fitness[Other Term]) OR walk test[Other Term] OR walk tests[Other Term]) OR strength [Other Term]) OR gait[Other Term] gaits[Other Term]) OR postural balance[Other Term] OR postural balances[Other Term]) OR standing balance[Other Term]) OR balance test[Other Term] OR balance tests[Other Term]) OR balance impairment[Other Term]) OR activity of daily living[Other Term] OR activity of daily life[Other Term] OR activities of daily living[Other Term] OR activities of daily life[Other Term]) OR standing test[Other Term] OR standing tests[Other Term]) OR timed up and go test[Other Term] OR timed up and go tests[Other Term])) OR comprehensive geriatric assessment[Other Term]) OR geriatric evaluation and management[Other Term]) OR frail[Other Term] OR frailty[Other Term]) OR fall[Other Term] OR falls[Other Term]) (5411)
7 ((((((((((((((((((Exercise[Title/Abstract] OR Exercises[Title/Abstract]) OR Physical performance[Title/Abstract]) OR Physical mobility[Title/Abstract]) OR Physical endurance[Title/Abstract]) OR Physical fitness[Title/Abstract]) OR walk test[Title/Abstract] OR walk tests[Title/Abstract]) OR strength[Title/Abstract]) OR gait[Title/Abstract] gaits[Title/Abstract]) OR postural balance[Title/Abstract] OR postural balances [Title/Abstract]) OR standing balance[Title/Abstract]) OR balance test[Title/Abstract] OR balance tests[Title/Abstract]) OR balance impairment [Title/Abstract]) OR activity of daily living[Title/Abstract] OR activity of daily life[Title/Abstract] OR activities of daily living[Title/Abstract] OR activities of daily life[Title/Abstract]) OR standing test[Title/Abstract] OR standing tests[Title/Abstract]) OR timed up and go test[Title/Abstract] OR timed up and go tests[Title/Abstract])) OR comprehensive geriatric assessment[Title/Abstract]) OR geriatric evaluation and management[Title/Abstract]) OR frail[Title/Abstract] OR frailty[Title/Abstract]) OR fall[Title/Abstract] OR falls[Title/Abstract]) (161461)
8 5 OR 6 OR 7 (464972)
9 4 AND 8 (1429)

EMBASE search strategy

1 exp falling/ (32186)
2 exp orthostatic hypotension/ or exp orthostatic stress/ or exp orthostatic blood pressure/ (19527)
3 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kw. (1449)
4 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (9595)
5 or/2-4 (22485)
6 exp physical performance/ or exp physical mobility/ or exp "physical activity, capacity and performance"/ or exp exercise/ or exp exercise test/ or exp body equilibrium/ or exp endurance/ or exp fitness/ or exp hand strength/ or exp muscle strength/ or exp grip strength test/ or exp balance impairment/ or exp daily life activity/ or exp activity of daily living assessment/ or exp geriatric assessment/ or exp frail elderly/ or exp falling/ (994777)
7 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (718598)
8 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kw. (53323)

9 or/6-8 (1523611)
10 5 and 9 (5009)

Appendix B. Specified Newcastle Ottawa Scale

Note: A study can be given a maximum of one point for each numbered item within the Selection and Outcome categories. A maximum of two points can be given for Comparability

Selection (S)

1 Representativeness of the exposed cohort with orthostatic hypotension
  a Subjects representative of the average subjected aged 65 years and older with orthostatic hypotension *
  b Not representative or no description
2 Selection of the non-exposed cohorts: subjects without orthostatic hypotension from the same community
  a Yes *
  b No
  c No description of the derivation of the non-exposed cohort
3 Ascertainment of exposure: how is orthostatic hypotension diagnosis made
  a Blood pressure measured both continuously and intermittently *
  b Blood pressure was measured continuously *
  c Blood pressure measured intermittently
  d No description or unclear
4 How was orthostatic hypotension defined?
  a Based on consensus definition of OH (SBP drop > 20 mmHg or DBP drop > 10 mmHg) *
  b Other
  c Not specified

Comparability (C)

1 Comparability of cohorts adjusted for potential confounders with respect to physical functioning
  a The study controls for: age, sex or both*
  b Study controls for any other factors, e.g. medication (e.g. antihypertensives, ACE inhibitors, beta blockers) and co-morbidities (e.g. Parkinson) *
  c Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome (O)

1 Assessment of physical functioning outcome
  a Objectively: by healthcare professional or measured using device *
  b Self-reported retrospective
  c No description
  d Other
2 Was follow-up long enough
  a Yes, > 6 months *
  b No, < 6 months
  c No follow up in study
3 Adequacy of follow-up of cohorts
  a Complete follow up- all subjects accounted for *
  b Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed *
  c Follow up rate less than 80% and on description of those lost
  d Not described or not applicable

SBP: systolic blood pressure; DBP: diastolic blood pressure; * = one poin

Appendix C

See Table C1.

Table C1
Physical functioning data.

First author	Physical functioning categories	Physical functioning data	Adjustments
Community-dwelling			
Ensrud et al., 1992	ADL	OH and impaired functional status (walking, climbing stairs, preparing meals, doing housework, shopping): OR 0.76 (CI 0.67-0.86)	Age
Formes et al., 2010	Exercise tolerance	No significant differences in MAP response to LBNP in group with high exercise tolerance (peak O2 uptake > 30 ml/min/kg) compared to group with low exercise tolerance (peak O2 uptake 18-28 ml/min/kg)	–
Guo et al., 2003	Balance, mobility and walking speed	Movement time (s) on postural-locomotor-manual test: 2.39 (OH+), 2.26 (OH-), p < 0.01. Baseline OH not associated with performance on postural-locomotor-manual test after eight years.	Prospective results were adjusted for baseline performance on postural-locomotor-manual test.
Kobayashi and Yamada, 2012	Walking speed; HGS	6-minute walk test (m): 498.4 (OH+, SD 80.4), 519.5 (OH-, SD 74.7), p = 0.972. HGS (kg): 26.7 (OH+, SD 7.7), 26.1 (OH-, SD 7.3), p = 0.559.	–
Mader et al., 1987	Balance	Postural symptoms (%; unsteadiness, dizziness) during standing: 21.9 (OH+), 18.3 (OH-), p > 0.05.	–
Masaki et al., 1998	Walking speed; HGS	Timed 10-foot walk (s): 4.79 (OH+), 4.31(OH-), p < 0.005. HGS (kg): 28.3 (OH+), 30.0 (OH-), p < 0.0001.	–
Matsubayashi et al., 2017	TUG; ADL	TUG (s): 16.4 (OH+, SD 4.5), 15.8 (OH-, SD 6.3), p > 0.05. ADL (walking, climbing stairs, eating, dressing, toileting, bathing, grooming and taking medicine; range from 0 [dependent] to 24 [independent]): 21.9 (OH+, SD 3.8) vs 23.2 (OH-, SD 1.8), p < 0.05.	–
Rockwood, 2012	Physical frailty	Fried frailty criteria (%): frail 8.0 (OH+), 6.7% (OH-), p = 0.058.	–
Romero-Ortuno et al., 2011	Walking speed; HGS; physical frailty; physical activity	Height normalized walking speed (m/s): 1.23 (OH+, SD 0.31), 1.22 (OH-, SD 0.22), p = 0.6. HGS (kg): 21.2 (OH+, SD 12.4), 20.6 (OH-, SD 11.9), p = 0.09. Fried frailty criteria (%): non-frail 44.0 (OH+), 57.7 (OH-), p = 0.17. pre-frail: 49.3 (OH+), 30.8 (OH-), p = 0.07, frail 6.7 (OH+), 11.5 (OH-), p = 0.41. Low physical activity (%): 17.5 (OH+), 11.5 (OH-), p = 0.39.	–
Rutan et al., 1992	Balance; mobility; ADL	OH prevalence (%): 20.7 (subjects with self-reported loss of balance), 17.4 (patients without loss of balance), OR = 1.18 (CI 0.99-1.40). OH prevalence (%): 22.3 (subjects with self-reported difficulty walking), 17.3 (subjects without difficulty walking), OR = 1.23 (CI 1.02-1.49). OH prevalence (%): 21.2 (subjects with self-reported ADL problems), 18.0 (subjects without ADL problems), OR 1.14 (CI 0.87-1.51).	Age and clinic site
Tang et al., 2012	Exercise tolerance	Peak VO2 consumption on graded max leg exercise test (ml/kg/min): 16.7 (OH-, SD 6.2), 18.1 (OH+, SD 8.3), p = 0.60.	Cholesterol and triglyceride levels
Tilvis et al., 1996	Exercise tolerance	Age- and sex adjusted prevalence of OH (%): 26.6 (subjects with NYHA class I, CI = 15.9-37.4), 40.1 (subjects with NYHA class III or IV, CI = 22.8-57.3).	Age and sex
Zhu et al., 2016	Mobility; physical activity	Need of walking aid in community (%): 25.0 (OH+), 16.6 (OH-). Physical activity during leisure (%): 74.4 (OH+), 65.7 (OH-).	–
Outpatients			
Aydin et al., 2017	Balance; gait; ADL	Tinetti balance score: 13.5 (OH-, SD 2.8), 13.2 (OH+, SD 3.2), p = 0.384. Tinetti gait score: 10.2 (OH-, SD 1.7), 10.1 (OH+, SD 1.8), p = 0.570. Basic activities of daily living score (0 - 100 [worst – best]): 91.5 (OH-, SD 13), 91.2 (OH+, SD 12.5), p = 0.856.	–
Cordeiro et al., 2009	Balance; TUG	Berg balance score: 50.48 (OH-, SD 5.85), 46.44 (OH+, SD 9.81), p = 0.021. TUG time (s): 14.8 (OH-, SD 5.79), 17.08 (OH+, SD 7.94), p = 0.144.	Balance was adjusted for age, sex, pain in lower limbs, ADL dependence, MMSE score and insulin use
Gaxatte et al., 2017	Balance; gait; TUG; ADL	Instability when standing upright or absence of postural reaction upon sternal pressure (%): 70 (OH-), 74 (OH+), p = 0.29. Gait disorder according to Alexander and Goldberg classification (%): 86 (OH-), 87 (OH+), p = 0.87. TUG time > 20 s (%): 58 (OH-), 64 (OH+), p = 0.20. Katz ADL score: 5.2 (OH-, SD 1.2), 4.9 (OH+, SD 1.4), p = 0.02.	–

(continued on next page)

Table C1 (*continued*)

First author	Physical functioning categories	Physical functioning data	Adjustments
Oishi et al., 2016	Balance; TUG	Self-reported symptoms of dizziness or loss of balance (%): 15.2 (OH-), 29.4 (OH+), p > 0.05. TUG time > 11 s (%): 73.7 (OH-), 46.7 (OH+), p < 0.05.	–
Pasma et al., 2014	Balance	OR OH and balance impairment on semi-tandem stance test with eyes closed: 3.03, p < 0.03*.	OR OH and balance impairment was corrected for age and sex.
Press et al, 2016	ADL	Barthel index: vs 84.7 (OH-, SD 15.9), 82.9 (OH+, SD 16.5), p = 0.25.	–
Soysal et al., 2014	Balance; gait; ADL	Tinetti balance score: 12.9 (OH-, SD 3.9), 11.9 (OH+, SD 3.7), p = 0.691. Tinetti gait score: 9.9 (OH-, SD 2.9), 9.8 (OH+, SD 3.1), p = 0.712. Basic ADL score (0-100 [worst-best]): 88.6 (OH-, SD 18.2), 84.6 (OH+, SD 21.0), p = 0.01.	–
Soysal et al., 2016	Balance	Postural symptoms of dizziness, sweating and imbalance (%) 48.9 (OH-), 45.6 (OH+), p = 0.576.	–
Susman, 1989	ADL	Parkerson functional score: 27.5 (OH-), 26.0 (OH+) p > 0.05.	–
Geriatric inpatients			
Aries et al., 2012	ADL	No quantitative data reported. No association between OH and modified Rankin scale 3 months after stroke.	–
Bendini et al., 2007	ADL	Katz ADL score: 5.1 (whole population, SD 1.0; no values for OH- and OH + group reported). Significant difference in ADL performance between OH- and OH + group, p = 0.028.	Age and sex
Coutaz et al., 2012	ADL	Barthel index (day 1-3 after hospitalization): 72.1 (OH-, SD 18.3) 69.3 (OH+, SD 20.0), p = 0.303.	–
Jodaitis et al., 2015	ADL	OH and decline in Katz score over last month: OR 2.46 (CI 1.51-4.00).	Feeling of fainting, syncope and recurrent falls
Kihara et al., 1998	ADL	Barthel index: 17.8 (OH-, SD 6.6), 23.3 (OH+, SD 10.0), p < 0.05.	–
MacLennan et al., 1987	Mobility	Mobility grading (1-11 [worst-best]): 7.5 (no SBP drop, SD 3.8), 7.5 (drop < 20 mmHg, SD 3.7), 8.1 (SBP drop > 20 mmHg, SD 3.6), p > 0.05.	–
Shen et al., 2015a, 2015b	Balance; gait; mobility; walking speed; HGS	Tinetti balance score: 13.7 (OH-, SD 1.48), 11.8 (OH+, SD 3.21), p = 0.003†. Gait disorder (%): 36.4 (OH-), 52.8 (OH+), p0.074. Use of walking aids (%): 10.0 (OH-), 19.4 (OH+), p = 0.119. Four-meter walk test (median in seconds): 6.5 (OH-, IQR 5.3-9.2), 6.0 (OH+, IQR 5.1-7.2), p 0.244. HGS (kg): 29.9 (OH-, SD 9.9), 27.9 (OH+, SD 9.0), p = 0.267.	Balance was adjusted for age
Siennicki-Lantz et al., 1999	ADL	Katz ADL index: Patients with Alzheimer dementia: 4.5 (OH-, range 1-7), 5.0 (OH+, range 3-6), p < 0.05. Elderly controls: 1 (OH-, range 1 - 1), 1 (OH+, range 1-2)	–
Vloet et al., 2005	Mobility	Self-reported mobility problems (%): 63.4 (OH-), 63.6 (OH+).	–
Nursing home residents			
Gray-Miceli et al., 2012	Balance	Loss of balance (% of no. of falls): 56.0 (OH-), 62.5 (near OH), 50.0 (OH+), 27.6 (OH not measured), p = 0.004.	–
Gray-Miceli et al., 2016	Balance; gait	Balance steady on initial standing (% of no. of falls): 43.4 (OH-), 22.2 (OH+), p = 0.09. Gait in steady line (% of no. of falls): 56.0 (OH-), 5.6 (OH+), p = 0.001.	–
Ooi et al., 1997	Mobility; ADL	Ambulation problem (%): 29.7 (OH-), 25.2 (Isolated OH), 26.7 (variable OH), 16.3 (persistent OH). p < 0.001. Arbitrary ADL score (higher scores indicating ADL independence): 1.7 (OH- SD 1.2), 1.6 (Isolated OH, SD1.4), 1.9 (variable OH, SD1.1), 1.8 (persistent OH, SD1.1). p = 0.60.	ADL was adjusted for age, sex, OH symptoms, BMI, medication, comorbidity and time of BP measurement
Patients with PD or parkinsonism			
Allcock et al., 2006	HY/UPDRS III	UPDRS III score (median): 17.0 (OH-, IQR 12.0), 19.0 (OH+, IQR 9.0), p = 0.08.	–
Ha et al., 2011	HY/UPDRS III	HY stage: Patients with PD: 2.39 (OH-, SD 0.86), 2.61 (OH+, SD 0.89), p = 0.01. Patients with atypical parkinsonism, without MSA: 2.90 (OH-, SD 1.07), 3.02 (OH+, SD 1.08), p = 0.77. Patients with MSA: 2.80 (OH-, SD 1.30), 3.50 (OH+, SD 1.26), p = 0.56.	–
Hohler et al., 2012	Balance; walking speed; TUG; ADL	Berg balance score: 29.58 (OH-, SD 13.01), 17.18 (OH+, SD 14.6), p = 0.019. Two-minute walk test (m): 206.1 (OH-, SD 80.1), 148.4 (OH+, SD 102.2), p = 0.059. TUG time (s): 42.9 (OH-, SD 28.9), 53.0 (OH+, SD 31.4), p = 0.304. Motor functional independence measure (self-care, sphincter control, transfers, locomotion; 13-91 [worst-best]): 30.0 (OH-, SD 10.82), 22.8 (OH+, SD 11.30), p = 0.044.	–

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Table C1 (*continued*)

First author	Physical functioning categories	Physical functioning data	Adjustments
Matinolli et al., 2009	Mobility; walking speed; TUG; physical activity; UPDRS II; HY/UPDRS III	Use of walking aids (%): 31.8% (OH-), 39.7% (OH+), p = 0.734 Walking speed (m/s): 1.2 (OH-, SD 0.3), 1.2 (OH+, SD 0.4), p = 0.806 TUG time (s): 13.2 (OH-, SD 7.8), 13.0 (OH+, SD 7.0), p = 0.865 High leisure time physical activity according to Pfaffenbarger questionnaire (%): 57.9% (OH-), 49.2% (OH+), p = 0.734 UPDRS II score: 12.9 (OH-, SD 5.9), 14.1 (OH+, SD 6.3), p = 0.732 UPDRS III score: 25.2 (OH-, SD 11.9), 24.4 (OH+, SD 10.0), p = 0.804	–
Matsui et al., 2006	HY/UPDRS III	UPDRS III score: 36.3 (OH-, SD 16.7), 32.8 (OH+, SD 15.8), p > 0.05.	–
Merola et al., 2016	mobility; ADL; UPDRS II; HY/UPDRS III	Ambulatory capacity measure (sum of items 13, 14, 15, 29, 30 of the UPDRS): 3.90 (OH-, SD 0.62), 6.07 (OH+, SD 0.83), p = 0.035*. Katz ADL score: 5.68 (OH-, SD 0.45), 4.74 (OH+, SD 0.51), p = 0.029 *. UPDRS II score: 10.19 (OH-, SD 6.91), 16.41 (OH+, SD 9.29), p = 0.041 *. UPDRS III score: 28.17 (OH-, SD 12.15), 33.27 (OH+, SD 14.38), p = 0.284 *.	Mobility, ADL and UPDRS II scores were adjusted for MOCA score and disease duration
Perez-Lloret et al., 2012	UPDRSII and HY/UPDRS III	Sum of UPDRS II and UPDRS III scores > 33 (%): 41 (OH-), 66 (OH+), p = 0.01. Adjusted OR = 2.21 (CI 0.81-6.07)	Age, polypharmacy, entacapone use, amantadine use, diuretics use
Sithinamsuwan et al., 2010	HY/UPDRS III	Frequency distribution of HY stage (%, 1 : 2 : 3 : 4 : 5) *OH-*: 36.7 : 28.6 : 28.6 : 4.1 : 2.0, *OH+*: 18.2 : 21.2 : 33.3 : 21.2 : 6.1, p = 0.003	–

OR: odds ratio; SD: standard deviation; CI: 95% confidence interval; MAP: mean arterial pressure; SBP: systolic blood pressure; LBNP: lower body negative pressure; MMSE: Mini Mental State Examination; MOCA: Montreal cognitive assessment; MSA: multiple system atrophy; NYHA: New York Heart Association classification of heart failure. *Data obtained by contacting authors. †Data extracted from figure.

Appendix D

See Table D1.

Table D1
Outcome measures of studies included in and excluded from the meta-analyses, per physical functioning category.

Physical functioning category	Outcome	Included studies	Excluded studies	Reason of exclusion
Balance	Tinetti balance score (C)	Aydin et al., 2017; Shen et al., 2015a, 2015b; Soysal et al., 2014	–	
	Berg balance score (C)	Cordeiro et al., 2009; Hohler et al., 2012	–	
	Balance impairment on semi-tandem stance test with eyes closed (D)	Pasma et al., 2014	–	
	Instability when standing upright or absence of postural reaction upon sternal pressure (D)	Gaxatte et al., 2017	–	
	Self-reported postural symptoms (unsteadiness, dizziness) and loss of balance during standing (D)	Mader et al., 1987; Oishi et al., 2016; Rutan et al., 1992; Soysal et al., 2016	Gray-Miceli et al., 2012, Gray-Miceli2016	Insufficient data reported
Gait characteristics	Tinetti gait score (C)	Aydin et al., 2017; Soysal et al., 2014	–	
	Gait disorder according to Alexander and Goldberg classification (D)	Gaxatte et al., 2017	–	
	Gait disorder (not specified) (D)	Shen et al., 2015a, 2015b	–	
Mobility	Need of walking aid (D)	Matinolli et al., 2009; Shen et al., 2015a, 2015b; Zhu et al., 2016	–	
	Mobility score assessing need of walking aids and help of other persons (C)	MacLennan et al., 1987	–	
	Ambulatory capacity measure (sum of items 13, 14, 15, 29, 30 of the UPDRS) (C)	Merola et al., 2016	–	
	Self-reported difficulty walking or mobility problems (D)	Ooi et al., 1997; Rutan et al., 1992; Vloet et al., 2005	–	
Walking speed	6-minute walk test (C)	Kobayashi and Yamada, 2012	–	
	2-minute walk test (C)	Hohler et al., 2012	–	
	4-meter walk test (C)	Shen et al., 2015a, 2015b	–	
	Walking speed (duration/distance not specified) (C)	Matinolli et al., 2009	–	
	Height normalized walking speed (duration/distance not specified) (C)	Romero-Ortuno et al., 2011	–	
	10-foot walk test (C)	–	Masaki et al., 1998	Insufficient data reported
TUG	Timed Up and Go time (C)	Cordeiro et al., 2009; Hohler et al., 2012; Matinolli et al., 2009; Matsubayashi et al., 2017	–	
	Timed Up and Go time > 20 s (D)	Gaxatte et al., 2017	–	
	Timed Up and Go time > 11 s (D)	Oishi et al., 2016	–	
HGS	Hand grip strength (C)	Kobayashi and Yamada, 2012; Romero-Ortuno et al., 2011; Shen et al., 2015a, 2015b	Masaki et al., 1998	Insufficient data reported
Physical frailty	Fried frailty criteria (D)	Rockwood et al., 2012; Romero-Ortuno et al., 2011	–	
Exercise tolerance	MAP as response to LBNP in group with high exercise tolerance (peak O_2 uptake > 30 ml/min/kg) compared to group with low exercise tolerance (peak O_2 uptake 18-28 ml/min/kg) (C)	–	Formes et al., 2010	Insufficient data reported
	Peak O_2 consumption on graded max leg exercise test (C)	–	Tang et al., 2012	Only study in this category
	Prevalence of OH in subjects with NYHA class III or IV compared to subjects with NYHA class 1 (D)	–	Tilvis et al., 1996	Insufficient data reported
Physical activity	Physical activity (time spent outdoor walking above/below 20th percentile of investigated population) (D)	Romero-Ortuno et al., 2011	–	
	Physical activity during leisure (not specified) (D)	Zhu et al., 2016	–	
	Physical activity during leisure (Pfaffenbarger questionnaire) (D)	Matinolli et al., 2009	–	

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Table D1 (*continued*)

Physical functioning category	Outcome	Included studies	Excluded studies	Reason of exclusion
ADL performance	Barthel index (C)	Coutaz et al., 2012; Kihara et al., 1998; Press et al, 2016	–	
	Katz ADL score (C)	Gaxatte et al., 2017; Merola et al., 2016	Bendini et al., 2007; Siennicki-Lantz et al., 1999	Insufficient data reported
	ADL scale assessing walking, climbing stairs, preparing meals, doing housework, shopping (D)	Ensrud et al., 1992	–	
	ADL scale assessing walking, climbing stairs, eating, dressing, toileting, bathing, grooming and taking medicine (C)	Matsubayashi et al., 2017	–	
	ADL scale assessing transfers, locomotion, self-care and sphincter control (C)	Hohler et al., 2012	–	
	Basic activities of daily living (not specified) (C)	Aydin et al., 2017; Soysal et al., 2014	–	
	Self-reported ADL problems (not specified) (D)	Rutan et al., 1992	–	
	Modified Rankin Scale (C)	–	Aries et al., 2012	Insufficient data reported
	Parkerson functional score (C)	–	Susman, 1989	Insufficient data reported
	Decline in Katz score over last month (C)	–	Jodaitis et al., 2015	Only study with longitudinal design
UPDRS II ADL performance	UPDRS II score (C)	Matinolli et al., 2009; Merola et al., 2016	–	
HY/UPDRS III performance	HY score (C)	Ha et al., 2011; Sithinamsuwan et al., 2010	–	
	UPDRS III score (C)	Allcock et al., 2006; Matinolli et al., 2009; Matsui et al., 2006; Merola et al., 2016	–	
Outcomes not classifiable into one physical functioning category				
Balance, mobility and walking speed	Postural-locomotor-manual test (C)	–	Guo et al., 2003	Outcome not classifiable into one category of physical functioning
UPDRS II ADL performance and HY/UPDRS III performance	Sum of UPDRS II and UPDRS III scores (C)	–	Perez-Lloret et al., 2012	Outcome not classifiable into one category of physical functioning

TUG: Timed Up and Go time; HGS: handgrip strength; ADL: activities of daily living; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr Scale; MAP: mean arterial pressure; LBNP: lower body negative pressure; NYHA: New York Heart Association classification of heart failure; C: continuous outcome; D: dichotomous outcome.

Appendix E. Supplementary forest plots showing subgroup analyses and individual study results

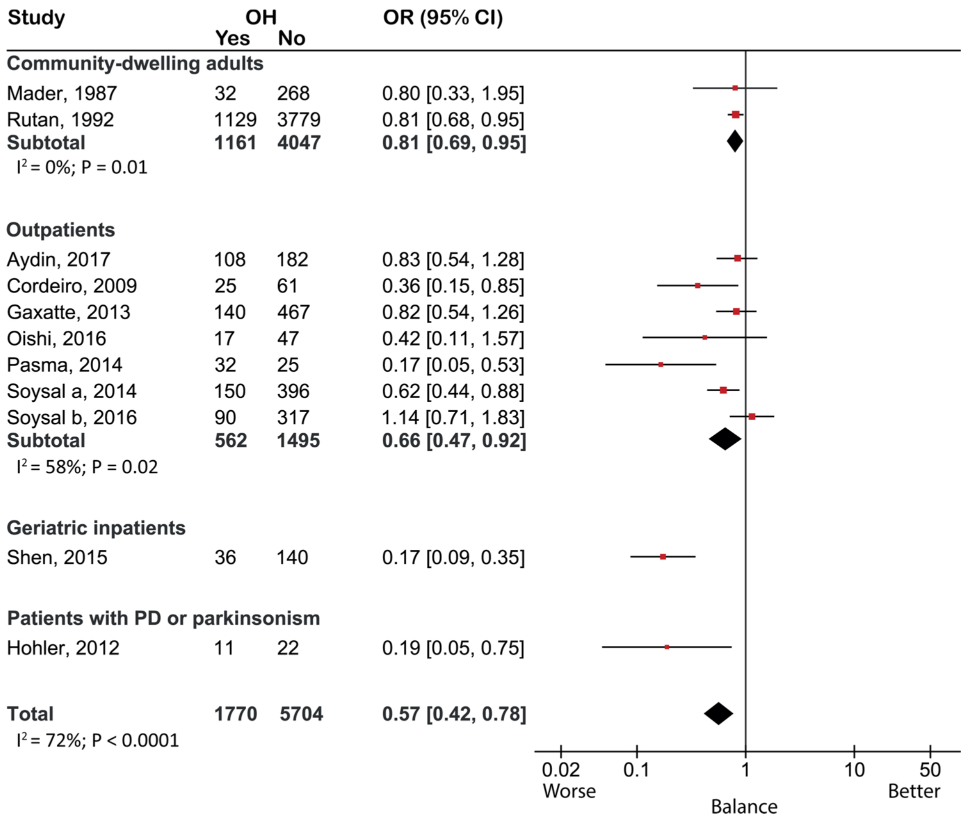

Fig. E1. Forest plot of studies investigating OH and balance. PD: Parkinson's disease.

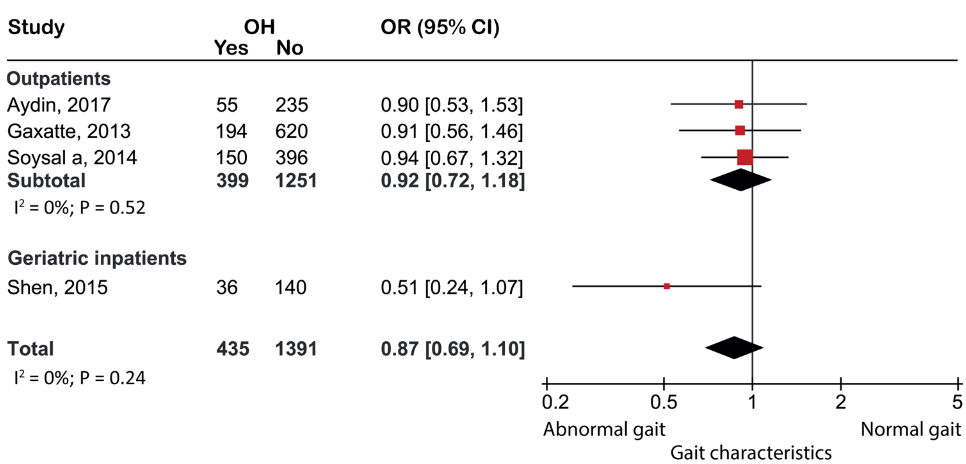

Fig. E2. Forest plot of studies investigating OH and gait characteristics.

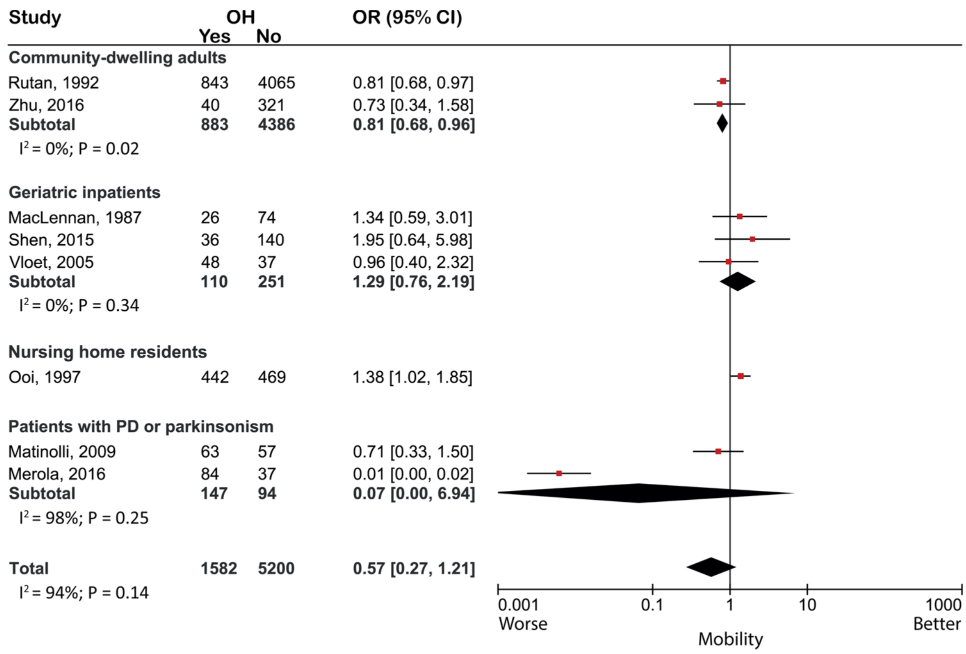

Fig. E3. Forest plot of studies investigating OH and mobility. PD: Parkinson's disease.

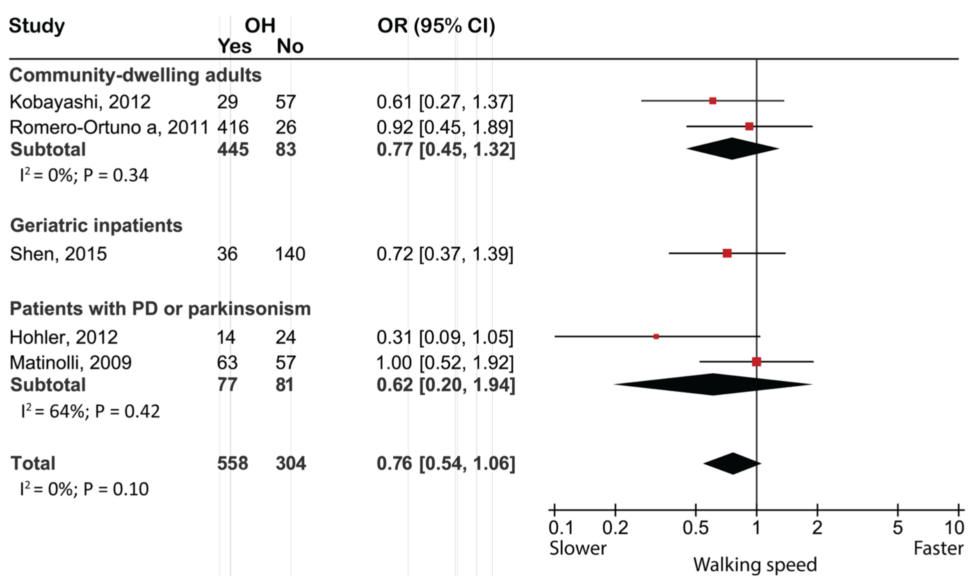

Fig. E4. Forest plot of studies investigating OH and walking speed. PD: Parkinson's disease.

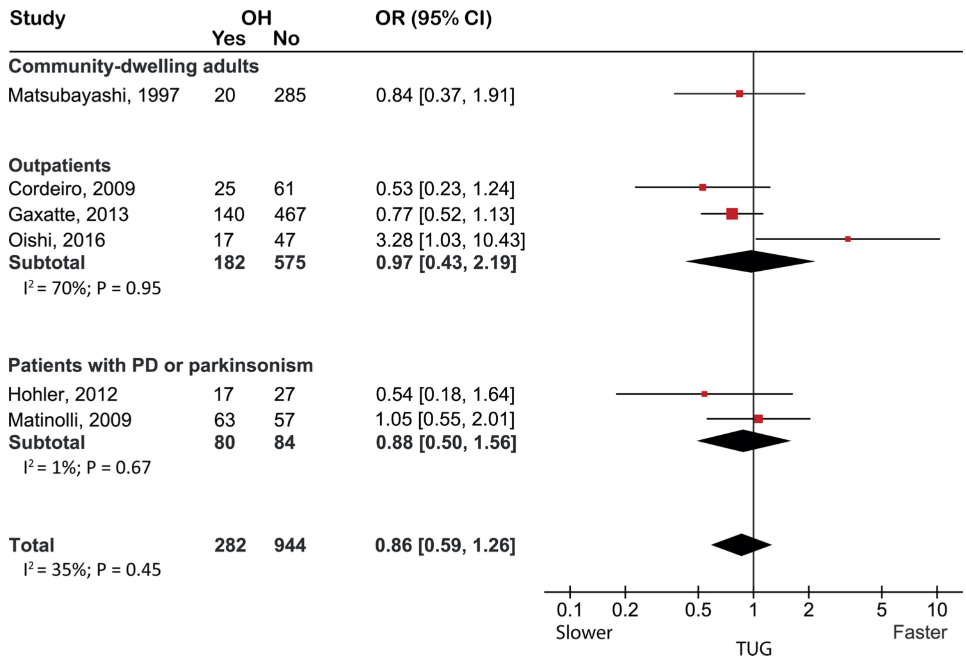

Fig. E5. Forest plot of studies investigating OH and Timed Up and Go (TUG) time. PD: Parkinson's disease.

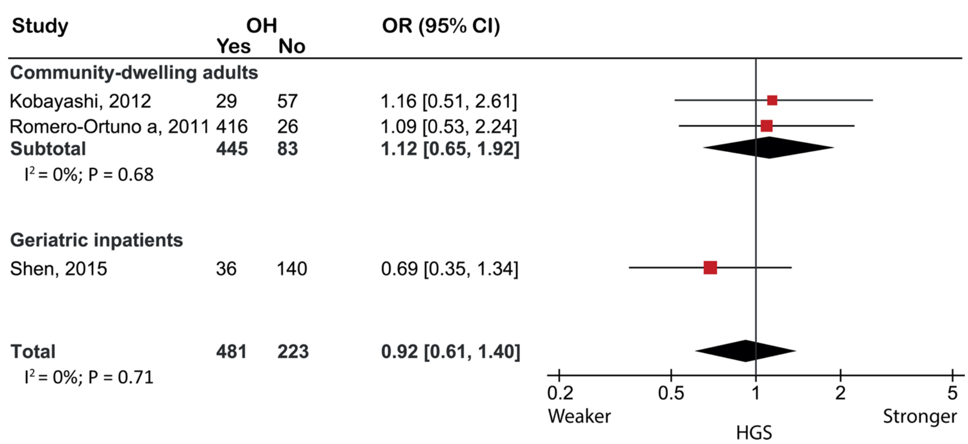

Fig. E6. Forest plot of studies investigating OH and hand grip strength (HGS).

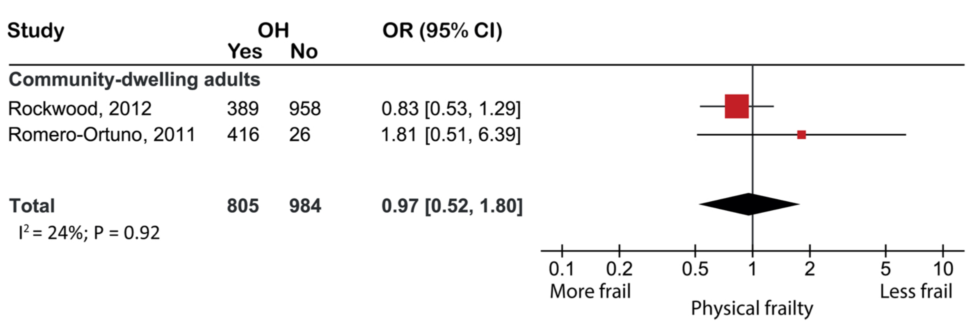

Fig. E7. Forest plot of studies investigating OH and physical frailty.

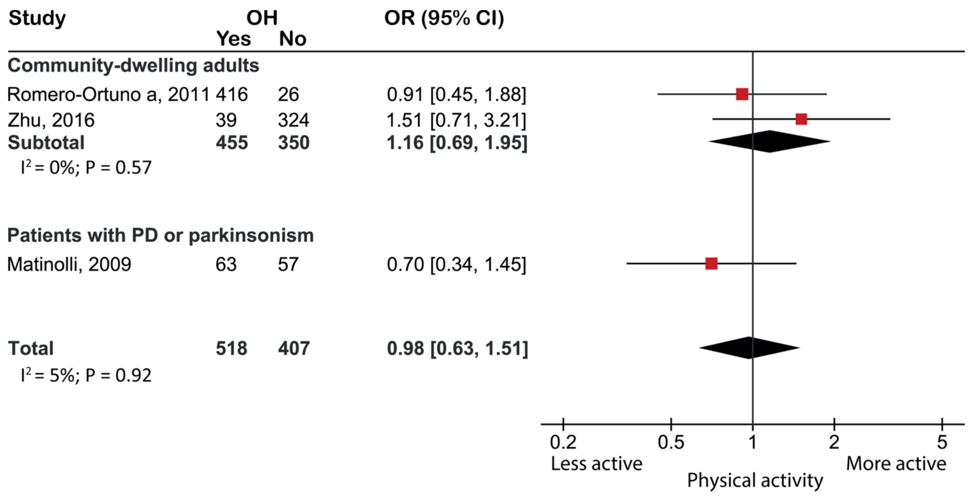

Fig. E8. Forest plot of studies investigating OH and physical activity. PD: Parkinson's disease.

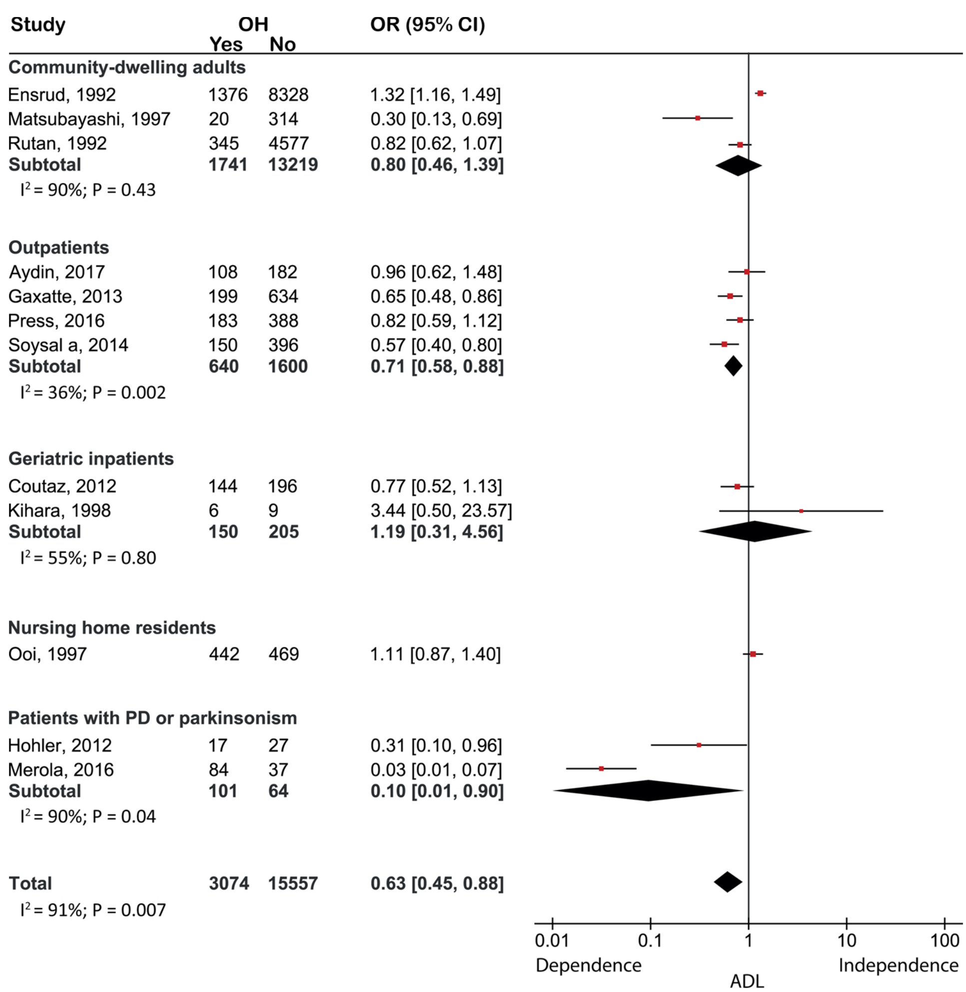

Fig. E9. Forest plot of studies investigating OH and activities of daily living (ADL). PD: Parkinson's disease.

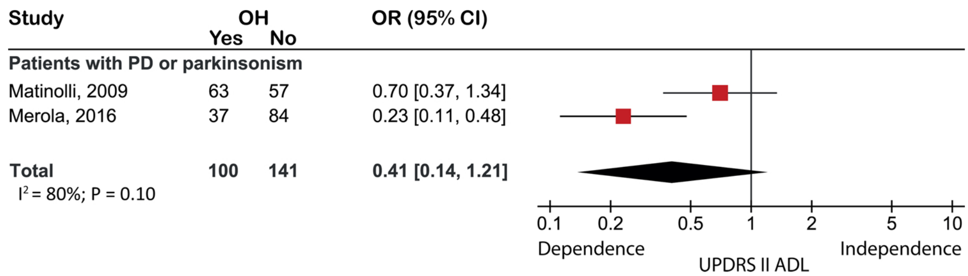

Fig. E10. Forest plot of studies investigating OH and activities of daily living (ADL) performance using the Unified Parkinson's Disease Rating (UPDRS) II scale. PD: Parkinson's disease.

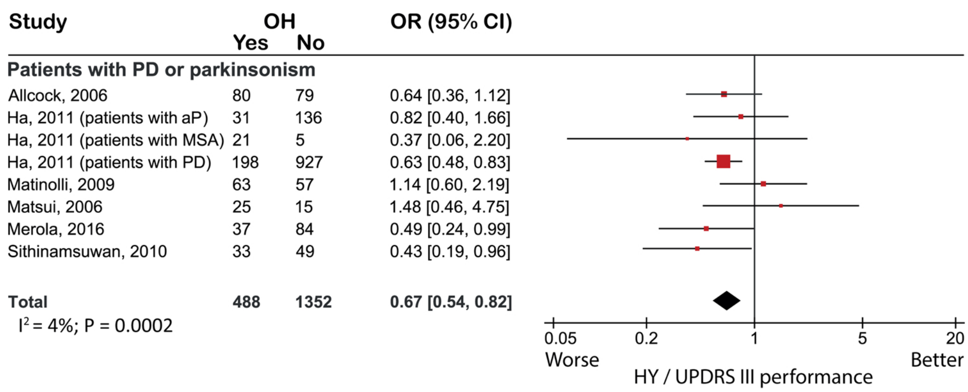

Fig. E11. Forest plot of studies investigating OH and performance on Hoehn and Yahr (HY) or Unified Parkinson's Disease Rating Scale (UPDRS) III scale. aP: atypical parkinsonism; MSA: multiple system atrophy; PD: Parkinson's disease.

Appendix F

See Table F1.

Table F1
PRISMA-P 2015 checklist.

Section and topic	Item No	Checklist item	Manuscript section (page)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title (1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Methods (5)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Authors, affiliations and corresponding author (1 and 2)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Author contributions (15)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Funding (2)
Sponsor	5b	Provide name for the review funder and/or sponsor	Funding (2)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Funding (2)
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction (4)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Introduction (4)
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Study selection (5)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods (5)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix A (41-47)
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Study selection (5)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Study selection (5), study selection for meta-analysis (8)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data extraction (5-6)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Physical functioning categories (7)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Study quality (6)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Sudy selection for meta-analysis (8)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Meta-analysis (8)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Meta-analysis (8)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Meta-analysis (8)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Meta-analysis (8)

PRISMA-P checklist for the reporting of systematic review protocols.

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